REMARKS

A Request for Continued Examination under 37 C.F.R. § 1.114 hereby accompanies this Amendment and Reply.

Entry of the foregoing, re-examination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. §§ 1.111 and 1.114, are respectfully requested.

Applicants thank Examiner Gambel for the informal telephonic discussion held on March 27, 2003.

I. CLAIM STATUS

As correctly stated in the Office Action Summary, claims 1 and 18-27 were pending in this application when last examined. Claims 1 and 18-27 have been examined on the merits, and stand rejected.

II. FORMAL MATTERS

A. Objection to the Specification

The Specification has been objected to for allegedly containing faint or missing words. The Examiner has suggested that Applicants provide a substitute Specification correcting such deficiencies. See March 13, 2003, Official Action, page 2, Item 3.

As discussed during the informal telephonic discussion with Examiner Gambel on March 27, 2003, this objection to the Specification will be held in abeyance until there is an indication of allowable subject matter.

B. Applicants' Priority Date

Acknowledgment has been made for the claim of domestic priority under 35 U.S.C. §§ 120 and 121. However, the Examiner has indicated that the filing date of the instant claims is deemed to be the filing date of the priority application, PCT/US96/18807, filed November 21, 1996. The Examiner contends that the earlier filed priority applications allegedly do not provide written support for the instant invention. See March 12, 2003, Official Action, pages 2-3, Item 4.

Applicants respectfully traverse this position and again submit that it would be appropriate to accord the instant claims the benefit of, at least, the **November 21, 1995** priority filing date, which is the filing date of Application Serial No. 08/561,521, now U.S. Patent No. 5,840,299 ("the '299 patent").

It is well established that a priority application need not describe *ipsis verbis* the later claimed invention. Instead, for priority analysis, "[t]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" Ralston Purina Co. v. Far-Mar-Co, Inc., 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985), quoting In re Kaslow, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983); see also Forssmann v. Matsuo, 23 U.S.P.Q.2d 1549, 1550 (B.P.A.I. 1992); M.P.E.P. § 201.11(a).

In Ralston, one issue was whether claim language of "protein content of at least about that of solvent extracted from soybean meal" was supported by the language of the parent application directed to"soybean meal having a low fat and a high protein content." Ralston, 227 U.S.P.Q. at 179. The Federal Circuit held that the parent disclosure supported the latter claim language in that the parent disclosure when viewed with what was known in the art reasonably conveyed the protein content. Id. Similarly, the Federal Circuit held that the parent application, which disclosed a "high protein content" and a preferred lower level but no upper limit, and indicated that protein content could be adjusted, reasonably conveyed adjustment of the protein content in the latter application to levels above 50%. Id. The one instance in which the Ralston Court found that the parent application did not support the later filed claims occurred when the new "claims would convey new information to one skilled in the art." Id. Thus, all that is required is that the application **reasonably** convey to persons skilled in the art that, as of the filing date, the inventor had possession of the subject matter later claimed by him.

In the instant case, the '299 patent teaches a method of treating a disease by administering a pharmaceutical composition containing the humanized monoclonal antibody 21.6 (hereinafter "MAb 21.6"). See the '299 patent, claim 27. The '299 patent further discloses that the humanized MAb 21.6 is useful for treating rheumatoid arthritis

(hereinafter "RA"). The '299 patent, col. 14, l. 55 to col. 15, l. 2. Thus, the '299patent discloses a pharmaceutical composition comprising said humanized MAb that is useful for treating RA. The instant claims are directed to a medicament and/or pharmaceutical composition comprising the humanized MAb useful for treating RA. Consequently, Applicants' prior application **reasonably** conveys to one skilled in the art that the Applicants had possession of a medicament and/or pharmaceutical composition comprising the humanized MAb useful for treating RA. In other words, there is more than adequate support for the claims of the instant application, drawn to a method of using the humanized MAb 21.6 for manufacturing a medicament for treating RA.

Furthermore, the Examiner's position would seem to require that the priority application describe *ipsis verbis* the later claimed invention. However, as stated above, the Patent Law does not require this. Moreover, to require such, would effectively turn all continuation-in-part practice ("CIP") into new priority filings, and thus, turn CIP practice on its head. Patent applicants are allowed and encouraged to file CIP applications including new information. Despite the new information, they are entitled to the effective filing date of the earlier application if the earlier application contains a written description such that it **reasonably** conveys to one skilled in the art that the Applicants had possession of the claimed invention. M.P.E.P. § 201.11(a). Thus, there is no need for the priority application to describe *ipsis verbis* the later claimed invention.

Finally, the rejection fails to set forth why one skilled in the art would not recognize the description in the earlier applications of pharmaceutical compositions comprising the humanized MAb. It is well established that the Patent Office has the initial burden of presenting evidence and/or reasoning as to why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. In re Wertheim, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976). In the instant case, the rejection fails to present adequate reasoning as to why one skilled in the art would not recognize the description in this earlier application of a pharmaceutical composition comprising the humanized MAb for the treatment of RA.

Thus, for the reasons set forth above, the instant claims should be accorded the priority benefit of, at least, the **November 21, 1995** filing date.

C. Drawings

The Examiner has acknowledged that the formal Drawings filed with the Amendment and Reply of October 24, 2002 comply with 37 C.F.R. § 1.84. See January 13, 2003, Official Action, page 3, Item 5.

D. Objections and Rejections Withdrawn

The objections to the Title and to the Drawings have been withdrawn in view of the Amendment and Reply filed October 24, 2002.

Likewise, the rejections of claim 17 under 35 U.S.C. §§ 112, first and second paragraph, the rejection of claim 1 under 35 U.S.C. § 102(e) as allegedly anticipated by Wayner *et al.*, and the rejection of claims 1 and 17-26 under 35 U.S.C. § 103(a) as allegedly obvious over Wayner *et al.* in view of Monshizadegan *et al.* or Yednock *et al.* U.S. Patent No. 5,530,101 and further in view of known methods to humanize antibodies as taught by Queen et al. Bendig *et al.* and Kettleberough *et al.* have been withdrawn in view of the Amendment and Reply filed October 24, 2002.

III. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1 and 17-27 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wayner *et al.* U.S. Patent No. 5,730,978 ("Wayner") in view of Bendig *et al.* WO 95/19790 ("Bendig"). See January 13, 2003, Official Action, pages 4-6.

Applicants respectfully traverse this rejection for the reasons previously set forth in the Amendment and Reply dated October 12, 2002, and for the reasons discussed herein below.

A. No Suggestion/Motivation To Either Modify or Combine the References' Teachings To Arrive at the Claimed Invention

The cited prior art fails to render obvious the claimed invention, because the references fail to provide at least the requisite suggestion/motivation to either modify and/or combine the reference teachings to arrive at the claimed invention.

It is well established that there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner previously relied on Bendig as providing the requisite suggestion/motivation for combining the references to arrive at the claimed invention. However, Bendig is directed to the use of the particular humanized 21.6 antibody to treat multiple sclerosis ("MS"), not RA. The Examiner argued that Bendig teaches testing in laboratory animals having experimental allergic encephalomyelitis ("EAE") which the Examiner contends was a known animal model for arthritis in addition to MS at the time of filing. See May 24, 2002, Official Action, page 7.

However, as previously argued this conclusory statement was **not** supported by either the cited references or the knowledge known in the art at the time of the claimed invention. To this end, Applicants submitted the following five journal articles highlighting the extensive differences between MS and RA, and further illustrating that at the time of the claimed invention, EAE and MS were not predictive for RA:

- Sadiq *et al* ., MERRITT'S TEXTBOOK OF NEUROLOGY, Chapter 128; Demyelinating Diseases, pp. 804-29 (Rowland ed., Williamd & Wilkins, Baltimore, 1995) ("Sadiq");

- El-Gabalawy *et al.*, ARTHRITIS RES., 4(suppl. 3): S297-S301 (2002) ("El-Gabalaway");

- Bergsteinsdottir *et al.*, JOURNAL OF IMMUNOLOGY, 164(3): 1564-1568 (2000) ("Bergsteinsdottir"); and

- Corthay *et al.*, INTERNATIONAL IMMUNOLOGY, 11:1065-1073 (1999) ("Corthay").

These references, which were previously submitted with the Amendment and Reply of October 24, 2002, show that at the time of the claimed invention that MS and RA were considered to be two completely different diseases with divergent etiologies and symptoms. First, MS is a chronic demyelinating autoimmune disease characterized by inflammatory

lesions along the myelin sheath of nerve fibers in the central nervous system ("CNS"). Second, MS is localized in the **CNS**. Third, a model of MS can be created by inducing autoimmunity by analogy to EAE. EAE is induced by immunization with the myelin basic protein. Despite the predictability of the therapeutic result by the correlation between the EAE model and MS, the etiology of human MS had not been completely elucidated at the time of the claimed invention.

By contrast, RA is an autoimmune disease that attacks connective tissue, primarily in the **joints**. In this disease condition, the immune system targets the cell lining in joints, **not** the cells of the nervous system as in MS. These references show that RA is believed to be caused by a yet **unknown** combination of genetic, environmental, hormonal, and reproductive factors. Despite intensive research, the cause of RA remains **obscure**.

Thus, while both diseases were classified as autoimmune diseases at the time of the claimed invention, there was no meaningful similarity between the two to suggest that an animal model for one would be a suitable model for the study of or predictive efficacy for the other disease. Histologically and anatomically the diseases are vastly different, thus, no artisan at the time of the claimed invention would have recognized the diseases or their models as correlative. At the time of the claimed invention, the etiologies and pathologies of both were unknown. Thus, those skilled in the art at the time of the claimed invention, and still today, would have reasonably believed that MS, as well as EAE are **different** and **distinguishable** from RA. Certainly, the skilled artisan would not have concluded EAE (and thereafter MS) to be analogous to RA. As such, EAE models and methods of treatment for MS would not have been predictive for RA. Any suggestion otherwise amounts to proceeding with no reasonable expectation of success.

The Examiner now contends that these references address only the differences in the genetic underpinnings of MS and RA and not the commonality of targeting α4 to inhibit the inflammatory response associated with both diseases. The Examiner further argues that Applicants have not addressed the alleged teachings of the prior art drawn to inhibiting the common deleterious inflammation of a number of inflammatory and autoimmune disorders, such as MS and RA by targeting leukocytes with α4-specific antibodies.

Applicants respectfully traverse the Examiner's position regarding the alleged obviousness regarding the commonality of targeting leukocytes with α4-specific antibodies to treat a number of inflammatory diseases and autoimmune conditions. The alleged commonality of targeting leukocytes with α4-specific antibodies to treat a number of inflammatory disorders fails to provide the requisite suggestion or motivation to combine the references to arrive at the claimed invention with a reasonable expectation of success.

For the Examiner's position regarding the commonality of targeting leukocytes with α4-specific antibodies to treat a number of inflammatory disorders to hold true, there must have been a suggestion of a common mode of inflammation between MS and RA. In other words, the inflammatory responses for both disorders had to have been sufficiently similar to have been predictive for one another. The cited prior art clearly does not provide such a suggestion. The cited references only discuss the inflammatory response associated with MS.

Regarding this alleged commonality, the Examiner has cited Lafaille *et al.*, J. EXP. MED. 186: 307-312 (1997) as allegedly teaching that "it was known in the art that pathogenic and protective roles have been ascribed to Th1 cells in inflammatory autoimmune diseases such as multiple sclerosis, diabetes and rheumatoid arthritis. . . ." See January 13, 2003, Official Action, page 4, Item 8. However, this reference is irrelevant to an obviousness analysis, because it post-dates the time of the claimed invention. It is well established that predictability is determined at the time of the claimed invention. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986); M.P.E.P. § 2143.03. Thus, whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made, not afterwards. Accordingly, this reference does not reflect the true state of the art at the time of the claimed invention.

Furthermore, even if Lafaille predated the claimed invention, the reference would remain irrelevant. In this regard, there are only two sentences in Lafaille that **hypothesize** that chronic inflammatory autoimmune disorders including MS and RA are caused by CD4+ Th1 cells. See Lafaille, Introduction, second sentence; page 307, sentence bridging

the first and second column. The remainder of Lafaille discusses the potential role of Th1 and Th2 cells in EAE. More importantly, Lafaille further indicates that the mechanisms by which Th1 and Th2 induce EAE in mice are **unknown**. Lafaille, page 310, first column, first sentence. Consequently, Lafaille provides further evidence that the mechanisms of inflammation in MS remain obscure. Thus, if anything, Lafaille supports the position that EAE is not a predictive model for RA.

The Examiner also cited Bekkum, J. CLIN. IMMUNOL., 20: 10-16 (2000) as allegedly teaching that experimental models of autoimmune disease can rely upon induction by immunization with specific tissues, such as basic myelin protein for EAE and collagen for arthritis. See January 13, 2003, Official Action, page 4. Similar to the Lafaille reference discussed above, this reference is irrelevant to an obviousness analysis, because it too post-dates the time of the claimed invention. Furthermore, this reference teaches that there are **separate** animal models for the various autoimmune diseases, *e.g.*, adjuvant arthritis ("AA") for arthritis and EAE for MS. Accordingly, Bekkum further supports the position that an animal model for MS would not be correlative, let alone predictive for RA.

Moreover, the state of the art **at the time of the claimed invention** clearly does not support the Examiner's position regarding the alleged obviousness of the commonality of targeting leukocytes with α4-specific antibodies to treat a number of inflammatory diseases and autoimmune conditions. In this regard, Applicants provide the following journal articles as evidence that at the time of the claimed invention, the inflammatory responses for MS and RA were unknown and clearly not predictable:

- Yednock *et al.*, NATURE, 356:63-66 (1992) ("Yednock");
- Fischer *et al.*, SCAND. J. IMMUNOL., 38:158-166 (19930 ("Fischer");
- Issekutz *et al.*, CLIN. IMMUNOL. IMMUNOPATH., 67(3):257-263 (1993) ("Issekutz 1993"); and
- Issekutz *et al.* J. EXP. MED., 181:1197-1203 (1995) ("Issekutz 1995").

These references are indicative of the state of art at the time of the claimed invention.

As disclosed in the instant Specification and in Yednock, α4 integrin antibodies had been tested for their anti-inflammatory potential in animal models for MS. Specification,

page 2, lines 21-25; Yednock, page 63, Introduction. Yednock reported complete inhibition of lymphocyte and monocyte binding to inflamed brain vessels in the *ex vivo* assay and complete inhibition of immune cell migration into the brain. Yednock, page 63, Introduction. However, the Yednock reference, which is limited to MS, fails to teach that inhibition of α4 integrin by a humanized monoclonal antibody would provide a significant therapeutic effect against RA.

Fischer studied the spectrum of molecules and functional epitopes involved in the interactions of lymphocytes with synovial endothelium during RA. In particular, Fischer tested various antibodies against α4, CD44, L-selectin, β1, and β2 for their ability to inhibit the lymphocyte binding to the endothelium from RA patients. Fischer found that the α4β1 integrins not only were able to recognize a variety of different ligands, but also transmit signals influencing different adhesion pathways, depending on the epitopes engaged. Fischer, page 164, second column, first full paragraph. Moreover, Fischer indicated that further experimentation was necessary "to dissect the complex functional aspects of the α_4/β_1- integrin molecules in regulating interactions between lymphocytes and endothelial cells in various types of tissues." Fischer, page 164, second column, first full paragraph. Thus, Fischer is significant in that at it illustrates that at the time of the claimed invention, lymphocyte binding to synovial vessels in arthritic joints was complex, poorly understood, and not solely dependent upon α4.

Furthermore, Issekutz (1995) studied monocyte migration in experimental models of arthritis. Issekutz (1995) indicated that the "mechanisms required for monocyte migration across the vascular endothelium in joints is poorly defined." Issekutz (1995), page 1197, Abstract. Issekutz (1995) further found that monocyte migration to the joints was **not inhibited** by treatment of the animals with monoclonal antibodies to LFA-1, Mac-1, or VLA-4 alone, and was only **partially** (50%) inhibited in only the most arthritic joint. Issekutz (1995), page 1197, Abstract.

Similarly, Issekutz (1993) studied the effect of anti-α4 integrin antibodies to inhibit lymphocyte migration in arthritic joints of rats. Issekutz (1993), page 257, Abstract. This reference is significant in that it demonstrates that anti-α4 integrin antibodies only **partially**

blocked lymphocyte migration to arthritic tissue. Issekutz (1993), page 257, Abstract. More importantly, Issekutz (1993) states:

> Thus, there are major LFA-1/MAC-1-independent mechanisms of PMNL recruitment to arthritis which have **yet to be defined**. It is also clear that LFA-1 is **not an important** ligand for T lymphocyte migration to arthritic joints in rat adjuvant arthritis. Thus, further work to evaluate leukocyte-endothelial adhesion and migration mechanisms appear **warranted if we are to learn to control the untoward effects of such immunopathological responses**.

Issekutz (1993), page 262, second column, last paragraph (emphasis added).

These references, which are indicative of the state of the art at the time of the claimed invention, and when viewed in their entirety clearly demonstrate that lymphocyte binding to synovial vessels in arthritic joints was complex, poorly understood, and not solely dependent upon α4. Accordingly, the state of the art at the time of the claimed invention does not support the Examiner's position regarding the commonality of targeting leukocytes with α4-specific antibodies to treat a number of inflammatory diseases and autoimmune conditions. Prior to Applicants' claimed invention, there simply was no support for the notion that inhibition of α4 integrin by a humanized monoclonal antibody would provide a significant therapeutic effect against RA. In this regard, there were no *in vivo* demonstrations of functional efficacy (*e.g.*, reduced swelling in the joints or decreased bone damage).

Thus, contrary to the unsupported assertion made in the rejection, based on the state of the art at the time of the claimed invention, and as evidenced by the above-discussed references, there was no suggestion in the art at the time to combine and/or modify the references to arrive at the claimed invention. In other words, the skilled artisan would not have found it obvious to target leukocytes with α4-specific antibodies to treat RA based upon a treatment model for MS.

B. No Reasonable Expectation of Success

The cited prior art references also fail to provide a reasonable expectation of success.

It is well established that the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 231 U.S.P.Q. 375 (Fed. Cir. 1986). Moreover, whether the art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986).

As discussed above, the Issekutz (1993), Issekutz (1995) and Yednock references, and even the references provided in the Official Action, when viewed in their entirety, clearly demonstrate that MS and its animal EAE would not have been correlative and/or predictive for RA at the time of the claimed invention. As such, there was no reasonable expectation of success in combining and/or modifying the references to arrive at the claimed invention.

In fact, Applicants submit that the references provided actually teach away from the claimed invention.

It is well established that a prior art teaching must be considered as a whole including portions that "teach away" from the claimed invention. See M.P.E.P. § 2141.02; W.L. Gore & Associates, Inc., v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Moreover, it is well established that references cannot be combined where the references teach away from their combination. M.P.E.P. § 2145; In re Grasselli, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of non-obviousness. M.P.E.P. § 2145; In re Hedges, 228 U.S.P.Q. 685 (Fed. Cir. 1986).

In this case, the cited prior art references discuss MS and the EAE model for MS. The Yednock, which discusses MS, demonstrated that α4 integrin antibodies result in complete inhibition of lymphocytes and monocyte binding to inflammed brain vessels. However, Issekutz (1995) showed that monocyte migration to the joints was not inhibited by treatment of animal with monoclonal antibodies to LFA-1. Similarly, Issekutz (1995) taught that LFA-1 was not an important ligand for monocyte migration to arthritic joints.

By contrast, this ligand is involved in MS. Thus, the art, when viewed in its entirety, taught away from the use of α4 integrin antibodies as a therapeutic treatment of RA.

Finally, at best, it appears that the rejection employs an "obvious to try" rationale to arrive at the claimed invention. However, it is well established that in moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. In re O'Farrel, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Indeed, the proper test requires determining what the prior art would have led the skilled artisan to do. However, as discussed above, references fail to teach or suggest treating RA.

Thus, in view of the above, the claimed invention is not obvious over the cited references because the cited art references lack a suggestion to combine/modify the reference teachings to arrive at the claimed invention and do not contain a reasonable expectation of success at arriving at the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Jay F. Williams
Registration No. 48,036

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 14, 2003